Title

Paediatric Traumatic Brain Injury

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Abstract

Purpose of review: To provide a summary of recent developments in the field of paediatric traumatic brain injury (TBI)
Recent findings: The epidemiology of paediatric TBI with falling rates of severe TBI, and increasing presentations of apparently minor TBI. There is growing interest in the pathophysiology and outcomes of concussion in children, and detection of "significant" injury, arising from concern about risks of long term Chronic Traumatic Encephalopathy. The role of decompressive craniectomy in children is still clarifying.
Summary: Paediatric TBI remains a major public health issue

Keywords

Traumatic Brain Injury, Concussion, Biomarkers, Epidemiology, Neurointensive care

Introduction

Traumatic Brain Injury (TBI) remains a major paediatric public health problem. One of the features that distinguishes TBI from other forms of paediatric acquired brain injury is the very different severity pyramid. For every case of severe TBI, there are tens of moderate, and hundreds or thousands of mild or apparently trivial TBI. This creates huge problems both for epidemiology (creating robust case definitions) and for assessing outcomes after milder forms of TBI. An important paper published this year [1••] confirms other recent reports of TBI epidemiology trends with decreasing numbers of severe TBIs being replaced by increasing numbers of Emergency Department (ED) attendances for mild TBI.

The question "is there a TBI severity threshold below which long-term consequences are improbable?" is one of huge pragmatic importance. Whilst past attempts to address this question suggested that the severity threshold is high [2••], this has been increasingly challenged in recent years with the recognition that there can be significant consequences particularly of *repeated* mild injury. One important setting for such events is contact sport, and there has been an explosion of work in the last few years in Sports Related Concussion (SRC).

One important, long-running and still incompletely resolved question is the extent to which the morbidity seen after milder injury reflects the injury *per se* or confounding pre-morbid factors. It has long been recognised that certain groups are at increased risk of TBI: there are strong correlations with socioeconomic deprivation, and over-representation of prior behavioural traits such as impulsivity, hyperactivity, and risk-taking behaviour. This also complicates studies of late psychological and behavioural outcomes (see below). A traditional approach to this challenge has been to use children sustaining orthopaedic and other injuries as controls with the logic ~~is~~ that factors predisposing to accidental injury will be equally over-represented in these groups. McKinlay et al confirm the validity of an "other injuries to the head" control group [3•]. Such "other injury" groups will however experience indirect effects of accidental injury (such as emotional effects of hospitalisation on child and family) so other approaches will be needed to separate these out.

Concussion

One major trend in recent years has been the growing research interest in concussion, particularly in sports. Concern about the possible serious late consequences of repeated mild to moderate head trauma (Chronic Traumatic Encephalopathy, CTE) originally arose in boxing but have spread to most contact sports including American football, rugby and soccer. Research is facilitated by the feasibility of pre-injury psychological testing (e.g. of athletes at the start of a season), immediate pitch-side testing and sometimes video of the concussion incident itself. Sports regulatory authorities, colleges and other organisations are developing increasingly formalised "Return to Play" protocols [4•], although the monitoring and well-being of young people playing sport in more informal settings is less established [5•].

There remain many areas of debate in the field of paediatric concussion including the role of computerised pitch-side cognitive testing and use of biomarkers of injury (see below) [6]. The

significance of demonstrations of sub-clinical alterations of brain physiology, and whether such altered function has any relevance to risk of development of CTE, remains unclear. For now, concussion remains a clinical, symptom-based diagnosis [7•]. Management is based on rest (and a veto on return to play) until symptoms of headache, fatigue and psychomotor slowing have resolved [8]. Post concussive symptoms (PCS) are common up to two years after mild TBI with headache being commonest early, and irritability, forgetfulness and fatigue the commonest late symptoms [9]. Many of these symptoms have migraine-like qualities to them and respond to migraine treatments. A pre-injury history of migraine is a risk factor for prolonged PCS, at least in females [10], again raising uncertainty about the relevance of PCS to risks of late CTE. For more persistent PCS, preliminary evidence was published in 2018 of the effectiveness of cognitive-behavioural therapies targeting understanding of concussion, activity scheduling, sleep hygiene and cognitive reframing [11•] although some authors suggested such approaches may be counterproductive [12]. Informational, emotional and referral support for the family may be as important as therapy targeting the young person per se [13].

The extent to which concussion in the immature brain differs from adult concussion remains very poorly studied [14•].

ED Triage and blood biomarkers

The need to triage large numbers of apparently minor head injuries presenting to ~~Emergency Departments (~~EDs~~)~~ has been an ongoing area of research. Until recently, interest focused on identifying those children at risk of early neurosurgical deterioration (e.g. due to expanding extra- or subdural haematomas). Since such haematomas can only be reliably identified by computerised tomography (CT) imaging, this becomes a question of selecting children for CT. A number of clinical decision rules [15••, 16•] have been developed over the last decade although of necessity they prioritise sensitivity over specificity and concerns persist that this leads to large numbers of unnecessary CT scans (typically about 10% of the children attending ED) [17]. One important issue that has as yet received little attention is that the left-shift in the severity distribution curve of EDs attendances discussed above (larger numbers of less severely injured children) that has largely occurred since these rules were developed and validated, reduces the prior likelihood of significant intracranial pathology, which will aggravate the lack of specificity.

Attention has increasing turned to the potential of circulating blood-borne biomarkers of injury and the possibility that these may increase the sensitivity and specificity of detecting significant TBI. It should be noted however that "significant" TBI (e.g. at risk of PCS) is not necessarily the same as TBI requiring neurosurgical assessment. Most of these candidate biomarkers have been known for decades: evaluation of their utility in paediatric TBI is lagging validation in adults. 2018 has seen publication of an important meta-analysis addressing the utility of S100B [18••] in children who met clinical decision-rule thresholds for CT. A systematic review of a wider range of blood biomarkers including Glial Fibrillary Acidic Protein (GFAP) and Ubiquitin Carboxy-terminal Hydrolase L1 (UCH-L1) for a wider range of endpoints (e.g. development of PCS as well as significant CT findings) has also been published [19••]. A retrospective study suggests that plasma D-dimer levels may also have utility in reducing numbers of unnecessary CTs [20•]. Preliminary reports on the role of novel multivariate

metabolomic [21] and proteomic panels [22] (in adults) were also published in 2018/9.

Imaging biomarkers

TBI is by definition typically a diffuse brain injury. Whilst effects of focal haemorrhage, ischaemia, and inflammation can be pertinent to more severe injury, traumatic axonal disruption is the hallmark of mild injury: mild TBI is a "disconnection disease". Diffusion Tensor Imaging (DTI) typically using the Fractional Anisotropy (FA) signal can be used to infer axonal integrity and thus structural connection strength; and resting state functional MRI (rsfMRI) can be used to infer functional connectivity between regions based on temporal correlation of fluctuations in their BOLD signal.

Measures such as FA can be particularly useful in milder injury where white matter may appear normal on standard T1 and T2 sequences [23]. In such mild injury the reduced microstructural integrity reflected by DTI may become more evident over time [24]. Although quantitative DTI is not in routine clinical use, a useful paper suggests that presence of focal pathology in the basal ganglia can be used as a proxy for the presence of microstructural damage in normal-appearing white matter, at least in adult TBI [25]. Straightforward calculation of FA values in the corpus callosum in (adult) TBI correlates with cognitive dysfunction [26]. Ryan et al report the value of white matter structural integrity in predicting cognitive outcomes in more severe paediatric TBI [27] and Stephens et al provide preliminary evidence of the utility of rsfMRI for the same [28]. Multimodal imaging e.g. combining DTI derived FA data with magnetic resonance spectroscopy (MRS) neurometabolic data (e.g. reflecting membrane turnover) may have additional value [29–31•].

These advanced imaging methods are largely research tools only at present. An important review highlights the major limitations of the current evidence base in assessing clinical utility, including the highly selective nature of study populations and particularly the under-representation of young children [32••].

Modern network neuroscience perspectives allow interpretation of the effects of local disconnection on the integrity and function of the wider brain network which may increase understanding of mechanisms of clinical recovery after more severe injury [33•, 34]; and there is interest in newer MRI sequences in the evaluation of more severe TBI [35].

Management of severe TBI

Delivering an acutely injured child to a trauma centre with expertise in managing paediatric TBI improves survival [36•] although in many ways, the central paradigm of Intensive Care Unit (ICU) management has remained frustratingly unchanged over several decades, remaining one of maintaining cerebral perfusion pressure (CPP) in the face of causes of raised intracranial pressure (ICP), either through medical or surgical management [37–39]. Multimodality monitoring, including the utilisation of state-of-the-art technologies such as direct and near-infrared spectroscopy-derived brain oxygenation and cerebral microdialysis, is seen as essential to optimally manage ICP and CPP [38•].

Surgical management of severe TBI remains focussed on a) removing space occupying pathology such as haematomas, contusions and depressed skull fragments and b) maintaining a normal ICP (usually <20mmHg) and optimal CPP (>40-50mmHg) with CSF diversion or decompressive craniectomy (DC). DC remains controversial and its role, particularly in paediatric TBI, as yet incompletely defined [40]. There is concern from adult data that DC

converts deaths into very poor-quality survivals [41] although a recent paediatric meta-analysis was cautiously positive [42•]. Two-thirds of head-injured patients undergoing emergency cranial surgery will require the evacuation of an acute subdural haematoma. Determining whether primary DC in addition to haematoma removal in the hope of better managing anticipated brain swelling is the goal of the ongoing RESCUE-ASDH trial which currently has randomized >400 patients >16 years old [41].

Some of the controversy regarding use of DC in children relates to the difficulty of managing a child with a large cranial defect. Relatively common surgical complications include disrupted CSF dynamics (including hydrocephalus and hygromas), infection, seizures and syndrome of the trephined. Robust multicentre data collection initiatives have improved understanding of risk factors for these complications[43, 44]. Uncertainty persists regarding indications for and timing of DC in different TBI subtypes and optimum surgical technique.

A revision of the Brain Trauma Foundation ICU management guidelines for severe paediatric TBI has been published recently [45•] although high-quality evidence e.g. from randomised studies is notably absent. Although the evidence base for many interventions (such as routine ICP monitoring) remains of limited quality there is evidence that standardisation of care *per se* improves outcome [46, 47].

A recently reported secondary analysis of the "Cool Kids" trial found that initiation of nutritional support within 72 hours of TBI was associated with decreased mortality and favourable outcome[48].

The role of more speculative and exploratory treatment such as stem cells remains for now entirely unestablished [49, 50].

Post-acute rehabilitation

In the post-acute phase, rehabilitation remains the mainstay of the clinical response to TBI. Epidemiological papers confirm previous findings that motor outcomes after TBI are generally superior to some other forms of acquired brain injury particularly anoxic brain injury [51, 52]. They also confirm that improvements in gross motor function can continue for several years after severe TBI with ongoing intensive rehabilitation [53].

For many young people after TBI, it is the cognitive and behavioural morbidities that are more significant. The large majority of paediatric TBI survivors "walk and talk" and make superficially good recoveries, but experience characteristic, often unrecognised and underestimated cognitive deficits, the consequences of which tend to compound over the remaining years of development into adulthood and particularly affect education. These issues speak to the long-running debate around age-at-injury effects in TBI: whether any potential benefits of "greater plasticity" in the young brain are outweighed by the need to complete development, "make a year's progress every year", with an injured brain. Empirical evidence is harder to obtain than might be thought because of confounds between age and particular injury mechanisms and severity. An important study again suggested late outcomes of injury in the very young are poor [54•]. Although there is some limited evidence for the efficacy of intensive cognitive therapies to improve the targeted impairments, the evidence that the benefits of these techniques generalise into wider gains is very limited [55, 56]. The creation

of an optimised educational environment remains the primary approach to post-TBI cognitive support [57, 58].

For medical practitioners there have been useful reviews of post-traumatic epilepsy after moderate to severe paediatric TBI [59] and the role of stimulant medication in managing executive and other dysfunction after TBI [60•, 61]

Late Outcome

Characteristic cognitive problems after TBI include particularly in executive function and new learning, impulse control, and difficulty reading social situations and conversation (e.g. a tendency to interpret ironic, sarcastic or figurative comments over-literally) and difficulties in "emotional mindreading,"[62]. Such factors are important risk factors for aggressive and violent behaviour, and the association between past TBI and offending behaviour has long been recognised.

Previous studies and meta-analysis have confirmed very high rates of past history of TBI in the incarcerated prison population. There have been longstanding controversies as to whether these associations are causal, or whether the occurrence of the TBI is an epiphenomenon, reflecting the socioeconomic deprivation and other factors alluded to at the top of this review. A major review [63••] suggests that the relationship is more directly causal than previously suggested and this has major implications for public health and policy: identifying the TBI survivor population as a group deserving of psychological, emotional, and educational support. Return to work has long been recognised as an endpoint for successive rehabilitation in adult practice. The equivalent for children, return to education (RTE) requires outreach to educational professionals that sometimes fail to see the priority that these children and young people require. It also requires understanding as to how consequences of TBI can emerge over time in the years post injury and will most typically manifest first in the school setting. Educators thus need to be taught how to understand the picture that is developing slowly in front of them [64, 65].

Self insight into how and why a TBI has changed them is invaluable but by definition can be difficult to acquire (because it requires intact frontal lobe-supported abilities of self-reflection [66]). Parental coping is an important determinant of outcome [67–69]. Two important 2018 studies in mild and mild to moderate TBI [70•, 71•] confirmed previous findings that with increasing time post injury behavioural and other symptom reports relate progressively less to objective injury severity and more to child and family pre-injury psychological risk factors. Whilst likely challenging to change, they are at least injury-independent potential targets for intervention [72•].

Conclusion

Paediatric TBI remains a major public health problem, with complex interactions between injury and ongoing development of the immature brain.

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Conflicts of interest

None

Summary points

- **Rates of severe head injury in children are declining, but there is increased concern about outcomes of minor head injury and particulary sports-related concussion.**
- **TBI to the younger 'vulnerable' brain may have more detrimental neuropsychological effects than injury in later childhood and TBI in childhood may predispose to unlawful behaviour in adult life.**
- **Management of severe traumatic brain injury at dedicated paediatric trauma centres with standardisation of intensive care appears to improve outcomes, however the role of decompressive craniectomy in children is yet to be elucidated.**
- **Following traumatic brain injury, optimising the educational environment remains the primary approach to cognitive support.**

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